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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/486,069	06/07/1995	DEAN ENGELHARDT	ENZ-5(D8)(C2	6278

28170 7590 03/12/2002

ENZO DIAGNOSTICS, INC.
C/O ENZO BIOCHEM INC.
527 MADISON AVENUE 9TH FLOOR
NEW YORK, NY 10022

EXAMINER	
MARSCHEL, ARDIN H	

ART UNIT	PAPER NUMBER
1631	80

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/486,069	Engelhardt et al.
Examiner	**Art Unit**
Ardin Marschel	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *see list in action attachment*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *See attached list.* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☒ Claim(s) *See attached list.* is/are allowed.

6) ☒ Claim(s) *See attached list.* is/are rejected.

7) ☒ Claim(s) *See attached list.* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☒ Interview Summary (PTO-413) Paper No(s). 76

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

CLAIM LISTS FOR 08/486,069:

Pending claims:

569-595, 597-643, 645, 646, 648-651, 654-679, 681, 682, 684-687, 690-714, 716, 717, 719-747, 749-797, 800-803, 806-831, 833, 834, 836-839, 842-866, 868, 869, 871-899, 901-947, 949, 950, 952-955, 958-983, 985, 986, 988-991, 994-1018, 1020, 1021, 1023-1051, 1053-1099, 1101, 1102, 1104-1107, 1110-1135, 1137, 1138, 1140-1143, 1146-1170, 1172, 1173, 1175-1250, 1252, 1253, 1255-1258, 1260-1294, 1296-1407, 1409-1568, 1570-1612, and 1614-1766

Allowed claims:

569-595, 597-599, 601-603, 625-633, 671-679, 684-687, 690-708, 719-722, 726-747, 753-755, 777-785, 823-831, 833, 834, 836-839, 842-860, 871-899, 905-907, 929-937, 975-983, 985, 986, 988-991, 994-1012, 1023-1026, 1030-1051, 1057, 1058, 1082-1089, 1127-1135, 1137, 1138, 1140-1143, 1146-1164, 1175, 1176, 1247, 1700-1703, 1719-1722, 1729, 1742, and 1766

Rejected claims:

600, 604, 605, 608-611, 614-624, 643, 645, 646, 648-651, 654-670, 681, 682, 709-714, 716, 717, 723-725, 752, 756, 757, 760-763, 766-776, 786-797, 800-803, 806-822, 868, 869, 903, 904, 908, 909, 912-915, 918-928, 938-947, 949, 950, 952-974, 1013-1018, 1020, 1021, 1027, 1056, 1059, 1060, 1061, 1064-1067, 1070-1081, 1090-1099, 1101, 1102, 1104-1107, 1110-1126, 1165-1170, 1172, 1173, 1177-1210, 1213-1229, 1232-1246, 1248-1250, 1252, 1253, 1255-1258, 1260-1294, 1296-1407, 1409-1420, 1426, 1428, 1430, 1432, 1434-1459, 1462-1471, 1473-1488, 1491-1494, 1497-1568, 1570-1612, 1614-1699, 1704-1718, 1723-1728, 1730-1741, 1743, 1744, and 1749-1765

Objected to claims:

606, 607, 612, 613, 634-642, 749-751, 758, 759, 764, 765, 861-866, 901, 902, 910, 911, 916, 917, 1028, 1029, 1053-1055, 1125, 1211, 1212, 1230, 1231, 1421-1425, 1427, 1429, 1431, 1433, 1460, 1461, 1472, 1489, 1490, 1495, 1496, and 1745-1748

3/8/02

Applicants' arguments and amendments; filed 11/15/01, 11/20/01, 11/20/01, 12/6/01, 12/20/01, and 12/21/01; have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. They constitute the complete set presently being applied to the instant application.

NEW MATTER REJECTION:

Claims 617-620, 622, 623, 769-772, 774, 775, 921-924, 926, 927, 1073-1076, 1078, 1079, 1224, 1225, 1228, 1229, 1235-1238, 1240, 1241, 1341-1344, 1346, 1347, 1436-1444, 1500-1503, 1505, 1506, 1629, 1630, 1633, 1634, 1640-1643, 1645, and 1646 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that the chemical linkages composed of a olefinic bond, various amines, etc. between the Sig moiety of the claims and the Base moiety of the labeled nucleotide was originally disclosed in original claims 77-82 only regarding Sig-Base attachment and not for Sig attachment to either the furanose or phosphate moieties therein. Instant claim 617-620, 622, 623, 769-772, 774, 775, 921-924, 926, 927, 1073-1076, 1078, 1079, 1224, 1225, 1228, 1229, 1235-1238, 1240, 1241, 1341-1344, 1346,

1347, 1436-1444, 1500-1503, 1505, 1506, 1629, 1630, 1633, 1634, 1640-1643, 1645, and 1646; now, however, cite such specific olefinic etc. attachment linkers to either the furanose or phosphate moieties of the labeled nucleotides of nucleotide analogs of the instant invention. These newly set forth specific linker species between furanose or phosphate moieties therefore add NEW MATTER to the instant disclosure.

SCOPE OF ENABLEMENT REJECTION:

Claims 600, 604, 605, 608-611, 614-624, 643, 645, 646, 648-651, 654-670, 709-714, 716, 717, 752, 756, 757, 760-763, 766-776, 786-797, 800-803, 806-822, 868, 869, 903, 904, 908, 909, 912-915, 918-928, 938-947, 949, 950, 952-974, 1013-1018, 1020, 1021, 1056, 1060, 1061, 1064-1067, 1070-1081, 1090-1099, 1101, 1102, 1104-1107, 1110-1126, 1165-1170, 1172, 1173, 1177-1210, 1213-1229, 1232-1246, 1248-1250, 1252, 1253, 1255-1258, 1260-1294, 1296-1329, 1332-1407, 1409, 1410, 1473-1488, 1491-1494, 1497-1568, 1570-1612, 1614-1616, 1619-1634, 1637-1699, 1704-1718, 1723-1728, 1730-1741, 1743, and 1749-1765 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for being limited to furanose moieties as the SM structure in the instant claims, does not reasonably provide enablement for the generic limitation given as "sugar". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below

Reconsideration of the prosecution history has revealed that the previous amending of the claims to limit the SM or sugar moiety in the practice of the claimed non-radioactive nucleotide or nucleotide analog structures to furanose has been reamended back to "sugar" in amendment R, filed 5/23/00. Upon review of this amendment and supporting sugar structures revealed that only furanose sugar moieties are disclosed which form the structure in

oligonucleotides or polynucleotides which will hybridize such as in hybridization probes with reasonable specificity and affinity. It is also noted that the early biochemical textbook of Lehninger summarized the hybridized structure of nucleic acids such as DNA on pages 638-639 as a specific structure which is needed in order to permit the hydrogen bonding to properly occur. It is noteworthy that even though this textbook is over 30 years old the only notable hybridization probe backbone structure analog to be significantly utilized in biochemical reactions in that of peptide nucleic acids. These peptide nucleic acids, however, lack any sugar in the backbone, but rather utilize peptide bonds with spacing linkages and thus is not a nucleotide polymer. In summary, the broad "sugar" wording for the SM moiety in the instant claims does not predictably support hybridization assay practice beyond the more limited form being "furanose".

Claims 681, 682, 723-725, 909, 1027, 1059, 1260, 1744, and 1761 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 681, 682, and 1260 depend directly or indirectly from a canceled claim.

Claim 909 is vague and indefinite because it cites "said sugar or sugar analog" whereas claim 873 from which it depends

lacks any antecedent basis for said phrase. Clarification via clearer claim wording is requested.

Claims 723 and 1027 are unclear due to the depending from a higher numbered claim.

Claim 1059 is vague and indefinite due to a lack of antecedent basis for "said ... phosphate analog" due to no such analog being cited in claim 1025 from which claim 1059 depends.

Claims 1744 and 1761 are vague and indefinite in citing the selection of purine analogs wherein the options include pyrimidines. Clarification via clearer claim wording is requested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1411-1420, 1426, 1428, 1445-1449, 1451, 1454, 1455, 1463-1471, 1712, 1714-1718, 1727, 1760, and 1761 are rejected

under 35 U.S.C. § 102(e) as being clearly anticipated by Kourilsky et al.(P/N 4,581,333), or, alternatively, under 35 U.S.C. § 102(b) as being clearly anticipated by Kourilsky et al.(GB 2,019,408).

Kourilsky et al. discloses the preparation of an oligonucleotide or polynucleotide hybridization probe which has been modified with mercury in column 4, lines 2-6. A sample of DNA from blood (In column 6, lines 26-31, in vitro diagnosis via blood etc. samples is deemed to reasonably disclose samples from a living organism.) is then obtained and denatured in preparation for hybridization to the probe in column 4, lines 14-17. Then the probe is added to the sample under hybridization conditions followed by avidin/β-galactosidase addition as in column 4, lines 18-40. The avidin/β-galactosidase conjugate is capable of binding to or complexing with the non-radioactively detectable protein conjugate via biotin linked via cytochrome C bridges to the probe molecules. Non-hybridized probe reagent is separated (including by gel) followed by the detection of the probe DNA hybrids via the addition of a substrate for the enzyme, therein set forth as ONPG in column 4, lines 41-62. This method anticipates the above listed claims in that nonradioactive procedures are utilized throughout the method in the reference. It is also noted that the probe may be directed to the detection of a variety of infections including bacteria etc. as listed in

column 6, lines 18-46, as also required in certain instant claims. Genetic anomalies are also detectable as noted in column 6, lines 47-54, and required in instant claim 1426, for example. It is noted that the prior art of Kourilsky et al.(GB 2,019,408) disclosure, on pages 1-5 therein, of the above subject matter is equivalent to that of Kourilsky et al.(P/N 4,581,333). It is also noted that instant claim 1411 has been amended to remove any limitation as to why the non-radioactively detectable protein is capable of binding or complexing with the oligonucleotide or polynucleotide probe. This rejection was argued previously in the REMARKS of amendment R, filed 5/23/00, but is non-persuasive to prevent this rejection due to the further claim amending as compared to the claims as worded on 5/23/00. Further consideration reveals that even the claim wording of 5/23/00 of claim 1411, for example, should not have prevented this rejection because the second segment of the probe which is recognized by via a protein binding nucleic acid sequence does not contain any limitation as to what characteristic may bind such a protein. Thus, the modified probe of the references are deemed to containing protein binding sequence as previously worded in claim 1411 as well as the present claim wording wherein only some unlimited capability of protein binding or complexing is required to bind or complex a protein to the probe.

The following is a quotation of 35 U.S.C. § 103(a) which

forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1411-1417, 1419, 1428, 1430, 1432, 1434, 1435, 1440, 1441, 1444-1459, 1462-1471, 1712, 1714-1718, 1727, 1760, and 1761 are rejected under 35 U.S.C. § 103(a) as being unpatentable over either of Langer et al.[PNAS 78:6633(1981)] or Dale et al.[Biochemistry 14:2458(1975)].

On pages 6633-6637 the Langer et al. reference describes the synthesis and various characteristics of biotin-labeled polynucleotides and sets forth a reasonable expectation of success for the usage of such polynucleotides as probes in hybridization assays for target nucleic acids. The motivation and suggestion to actually perform such assays is supplied in the

DISCUSSION section on page 6637, last 4 line of the lefthand column through line 11 of the righthand column. In this same DISCUSSION section the motivation and suggestion to utilize non-radioactive protein which binds to the biotin-labeled probe is also set forth. Such non-radioactive proteins are listed as fluorescein labeled goat IgG with antibiotin antibody or antibody-phosphatase conjugates which bind or complex with probes during the assay for detection. Such IgG or antibodies are also well known to be glycosylated and therefore include a polysaccharide or monosaccharide therein. The biotin-probe with non-radioactive protein detection complex formation and detection thereof is deemed an embodiment of instant claims 1411 etc. It is noted as discussed above that instant claim 1411 does not limit the binding of complex formation mechanism between the probe and protein of the claim in any specific way so as to prevent this rejection. It is also noted that the target nucleic acids utilized in the reference are directed to the bacterial microorganism E. coli which is a target type required in certain instant claims. In said DISCUSSION section the suggestion of utilizing tissue sections is also set forth which motivates, therefore eukaryotic organisms as these are deemed to be the only organism type with tissue, which are also generally obtained from living organisms.

Thus, it would have been obvious to someone of ordinary

skill in the art at the time of the instant invention to practice the suggested and motivated hybridization assay as given in the reference to practice the instant invention with a reasonable expectation of success due to the various characterization experiments in the reference to document the usability of the biotin-labeled probes therein in various types of hybridization assay. Similarly, the Dale et al. reference describes the hybridization characteristics of mercurated probes and motivates and suggests their use in hybridization assays in the last sentence of the abstract therein.

Claims 1298-1305, 1315, 1318, 1320, 1324-1333, 1335-1340, 1345-1352, 1358, 1359, 1371, 1373, 1379, 1385-1390, 1399-1401, 1403, 1404, 1406, 1407, 1409, 1582, 1583, 1585-1591, 1593-1597, 1599, 1601, 1605-1609, 1611, 1612, 1614-1618, 1620-1639, 1644-1650, 1656, 1657, 1669, 1671, 1677, 1678, 1684-1688, 1695-1699, 1705, 1708, 1709, 1711, 1725, 1726, 1730, 1749-1751, and 1758-1761 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hartman et al.[Biopolymers 20:2635(1981)].

Hartman et al. suggests and motivates the use of methacrylate modified azoRNA in hybridization assays in the title and abstract. The abstract and EXPERIMENTAL section describe the preparation and analysis of said modified azoRNA as hybridization probes. The hybridization of probe to known chromosomal targets is described on page 2636, first paragraph, which is deemed a

type of karyotyping. On page 2641, a non-radioactive label structure at the C-4 position of cytidine is shown. These probes are made by the incorporation of semicarbazide-modified nucleotides as outlines on page 2639 which is additionally modified by the methacrylate in the reference. A reasonable expectation of success in using such a probe in hybridization assays include its measurement at 248 nanometers of UV absorption is shown on page 2644 in Figure 5 and elaborated in more detail in the DISCUSSION section on pages 2645-2647. These labels also include the binding or chelation of heavy metal atoms for detection as discussed on page 2637, lines 1-13, as also embodiments of certain instant claims. The use of these probes is also motivated by an increase in sensitivity as discussed in the bridging paragraph between pages 2636 and 2637 wherein radioactive or fluorescent detection methods are suggested to be replaced by the polymerization of methacrylate polymer at hybridization sites which binds markers.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the methacrylate polymerization type of hybridization assay with non-radioactive ribonucleotide probes as given in the reference to result in embodiments of the instant invention.

IDS

The receipt of the copies of references in the IDS, filed

10/9/01, is acknowledged. The German and Japanese documents, however, cannot be considered due to their unreadability in these languages. English translations are hereby requested.

Claims 606, 607, 612, 613, 634-642, 749-751, 758, 759, 764, 765, 861-866, 901, 902, 910, 911, 916, 917, 1028, 1029, 1053-1055, 1125, 1211, 1212, 1230, 1231, 1421-1425, 1427, 1429, 1431, 1433, 1460, 1461, 1472, 1489, 1490, 1495, 1496, and 1745-1748 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 569-595, 597-599, 601-603, 625-633, 671-679, 684-687, 690-708, 719-722, 726-747, 753-755, 777-785, 823-831, 833, 834, 836-839, 842-860, 871-899, 905-907, 929-937, 975-983, 985, 986, 988-991, 994-1012, 1023-1026, 1030-1051, 1057, 1058, 1082-1089, 1127-1135, 1137, 1138, 1140-1143, 1146-1164, 1175, 1176, 1247, 1700-1703, 1719-1722, 1729, 1742, and 1766 are allowed.

The Request for Interference, filed 12/21/01, is acknowledged as having been received and will be handled in due course.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)305-3014 or (703)308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tina Plunkett, whose telephone number is (703)305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

March 8, 2002

ARDIN H. MARSCHEL
PRIMARY EXAMINER